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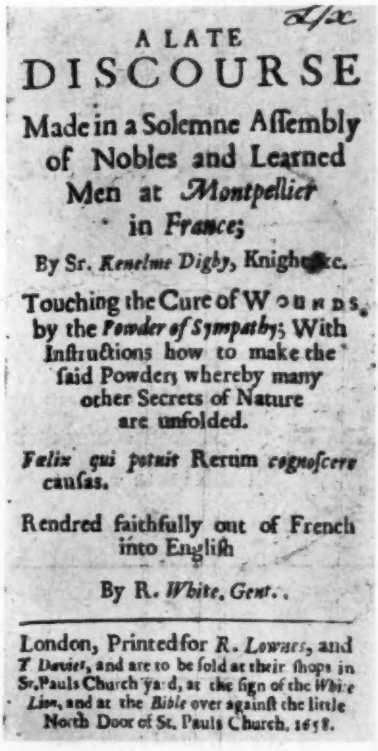

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Title page from Digby's discourse on the "Powder of Sympathy" (see page 63).

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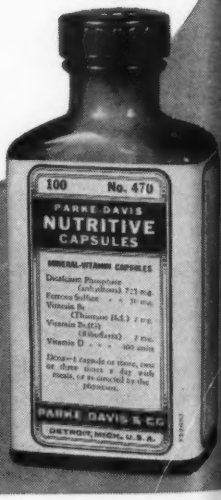

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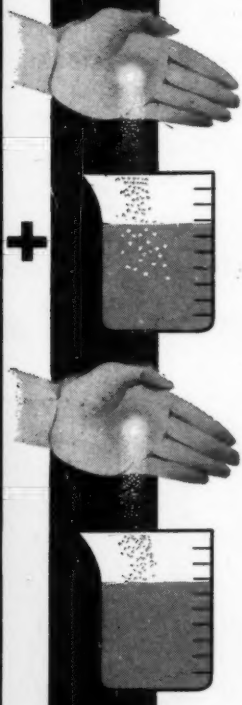

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EDITORIAL

A NATIONAL DISGRACE

AN article* which recently appeared in the Quarterly Bulletin of the Association of Food and Drug Officials, if its statements concerning Pharmacy are generally true, is both an indictment and a disgrace to Pharmacy of the first magnitude.

In this article the author reports the findings of the Massachusetts Department of Health on the analyses of a number of solutions prepared on order by pharmacists in that state. The findings, in the main, indicate an inaccuracy that is almost unbelievable and worst of all it would appear that the inaccuracy was based on either a willful desire to prepare a substandard solution, as a matter of increased profit, or the lack of sufficient ability on the part of pharmacists to calculate the required quantity of drug to prepare a given strength solution. Evidence of both conditions is cited in a very convincing manner.

Such simple solutions as 5 per cent potassium permanganate, 15 per cent argyrol, 5 per cent phenol, etc., were found to be below strength to the extent of 30 per cent of the total samples examined and a standard prescription filled in eighteen drug stores had an error of 10 per cent or more made in one or more ingredients in nine cases or 50 per cent of the stores visited. Other evidences of unprofessional conduct were cited as common, e. g., selling tap water for distilled water and cottonseed oil for olive oil.

The author makes no effort to explain such an unfortunate condition since as an enforcement official it is simply his duty to present the evidence, but pharmacists who read this paper, although ashamed of the record established in Massachusetts, will doubt that this condition exists to a like degree in all states of the union.

The state of Massachusetts, although one of the original colonies and in many respects a progressive state, is shamefully behind its neighbors in the matter of establishing minimum standards for pharmaceutical licensure. In spite of the fact that within the confines of

* Pharmaceutical Accuracy by H. C. Lythgol. *Quart. Bull. Assoc. Food & Drug Officials, 10,* 3 (1946).

the state there exists one of the finest colleges of pharmacy in the country, college training is still not a prerequisite to the state examinations qualifying one as a pharmacist. To make matters worse a "cram school" operates in Massachusetts and circulates literature throughout all the eastern states encouraging all the failures and misfits in pharmacy to qualify as pharmacists in this last stronghold of archaic standards! Is it any wonder then that many pharmacists in this unfortunate place are found to be uneducated and lacking in professional ideals and perspective?

Our sympathy extends to those honest and true pharmacists who are indicted with the muck within their profession and to the Massachusetts College of Pharmacy which has fought a long battle against such conditions. The politicians who have made this condition possible through expedient procrastination are a fine example of those who continue to betray their constituents for reasons known only to themselves.

Boards of Pharmacy which now are fighting to preserve standards of licensure in various other states may well use this concrete example of what may be expected if men without a college background and training are permitted to enter our profession. The medical profession which is very directly influenced by the standards of pharmaceutical practice should give us unqualified support in our efforts to establish and maintain pharmacy on that plane where accuracy and ethical conduct can be expected within the limits observed in the other fields of public health.

L. F. Tice.

THE DETERMINATION OF BARBITURATES IN TOXICOLOGICAL AND CLINICAL INVESTIGATIONS *

By Eugene L. Cohen

Introduction

IN 1924, Parri (1) proposed a colorimetric test for barbituric acid and its derivatives based on the reaction of cobaltous compounds with the barbiturate in an alkaline medium. Zwikker (2), in 1931, suggested the use of cobaltous chloride and barium oxide as the reagents. Later, Bodendorf (3) substituted cobaltous nitrate for the chloride and potassium hydroxide for barium oxide. In 1934, Koppanyi and his co-workers (4) (5) modified the test using cobaltous acetate and isopropylamine as the reagents. Kozelka and Tatum (6) and other workers made minor variations, the former using sodium ethylate as the alkalinizing agent. It soon became apparent from the studies reported that the final color reaction could be obtained regardless of the cobalt salt used and also that different alkalinizing agents could be employed.

The color reaction produced by the interaction of the barbiturates with the cobalt salts in alkaline medium is not specific. The same end color compound is produced with other substances, such as phthalimide, theobromine or theophylline. This non-specificity, however, does not destroy the usefulness of the reaction for toxicological purposes. All qualitative determinations are verified by corroborative tests such as the mercuric nitrate and silver nitrate tests given in the United States Pharmacopœia XII (7) or the mercurous nitrate, potassium iodide, and ferric chloride differentiation tests as reported by Motley (8).

The tests mentioned are not specific for the individual barbiturates, though they will, as noted below, yield some information along these lines. The tests are essentially barbiturate group tests and are used primarily for differentiating the barbiturates from other compounds. Simply, these tests are as follows:

---

* A dissertation presented to the Faculty of the Philadelphia College of Pharmacy and Science, in partial fulfillment of the requirements for the Degree of Doctor of Science in Pharmacy.

1. Mercuric Nitrate Test: on the addition of a few drops of 4N mercuric nitrate solution a precipitate is formed which is soluble in an excess of 10% ammonia.
2. Silver Nitrate Test: on the addition of a few drops of 0.1N silver nitrate solution a precipitate forms which is soluble in 10% ammonia.
3. Mercurous Nitrate Test: on the addition of 1 drop of a 15% mercurous nitrate solution in 5% nitric acid, a white to gray gelatinous or flocculent precipitate is formed. On the addition of 2 drops of a 1N solution of potassium iodide to the solution containing the precipitate, the precipitate changes to a fine greenish color.
4. Mercuric Nitrate—Potassium Iodide Test: on the addition of 1 drop of a 15% mercuric nitrate in 5% nitric acid a white precipitate is produced. If 2 drops of 1N potassium iodide solution are added to the precipitate, a clear solution is produced.

   Note: Seconal yields a hazy solution.
5. Mercuric Nitrate—Ferric Chloride Test: on the addition of 1 drop of a 15% mercuric nitrate solution in 5% nitric acid, a white precipitate is formed. If 2 drops of 10% ferric chloride solution are added to the precipitate, a clear solution is produced.

   Note: Seconal yields a hazy solution. Pentothal yields a white flocculent precipitate.
6. Cobalt Reaction: Add one drop of 1% cobaltous acetate in absolute methanol and 3 drops of 1% isopropylamine in absolute methanol. A reddish-violet color is produced.

Koppanyi (4) recommended that the color reaction reported by him be employed for semi-quantitative estimations of the barbiturates. Kozelka and his co-workers (9) did not agree with this viewpoint. Other workers (10) (11) suggested its use, if at all, for semi- or approximate quantitative purposes only.

Purpose

A review of the literature, as indicated above, revealed the inadequacy of available methods for estimating quantitatively the barbiturate content of animal tissues and fluids. Furthermore, satis-

factory procedures were not found in the literature for extracting all of the barbiturate found in materials under investigation. These studies were therefore undertaken (a) to determine whether the cobalt color reaction for barbituric acid and its derivatives could be used for the quantitative estimation of the barbiturates, and (b) to devise a procedure for the isolation and subsequent purification of the barbiturates from body tissues and fluids. The procedures to be made available were those which could be performed by the average technician employing the equipment commonly found in hospital and clinical laboratories.

Investigation

Part I

The Quantitative Aspect of the Barbiturate-Cobalt Reaction

The studies of the quantitative aspect of the barbiturate-cobalt color reaction included investigations of the relationship of the intensity of the end cobalt-barbiturate color compound to the barbiturate concentration, the optimal proportion and amounts of the reagents required in the test, and whether it was possible to employ just one known barbiturate as a positive control or standard for estimating quantitatively all of the barbituric acid compounds.

Experimental

Reagents required:

1. Chloroform (USP): dried over CP anhydrous calcium chloride or CP anhydrous sodium sulfate.

2. Cobaltous Acetate (ACS): a 1 per cent solution in absolute methanol (ACS). Care must be taken that moisture is eliminated from this reagent since the presence of even small amounts of moisture will interfere with color production. The cobaltous acetate was first dried for one hour at 100° C. and stored in a desiccator before use. The methanol was dried over anhydrous calcium chloride or anhydrous sodium sulfate. The reagent solution was prepared in 100 ml. quantities and stored in completely filled, paraffin-sealed, 25 ml. bottles.

3. Isopropylamine (Eastman Kodak Co.): a 1 per cent solution in absolute methanol. The same caution as to moisture applies to

this reagent. The isopropylamine was dried over anhydrous sodium sulfate. The amount prepared and the storage were as mentioned above under cobaltous acetate.

4. Barbiturates: the following barbiturates were used for these studies:

Barbital (USP)	(Diethylbarbituric Acid)
Phenobarbital (USP)	(Phenylethylbarbituric Acid)
Pentobarbital	(Ethyl (1-methylbutyl) barbituric Acid)
"Seconal" (Lilly)	(Allyl (1-methylbutyl) barbituric Acid)
"Pentothal" (Abbott)	(Ethyl (1-methylbutyl) thiobarbituric Acid)
"Amytal" (Lilly)	(Isoamylethylbarbituric Acid)
"Delvinal" (Sharp and Dohme)	(Ethyl 5-(1-methylbutenyl) barbituric Acid)

In the case of Barbital, Amytal and Phenobarbital the acid compound conforming to the formula given above was available. Pentobarbital, Delvinal, Pentothal and Seconal were available only in the sodium salts. The acid form as given above was prepared from the sodium salts by acidification and extraction of an aqueous solution with chloroform. All of the barbiturates were purified by the method described later.

5. Barbiturate Solutions: each barbiturate was dissolved separately in dry chloroform in a concentration of 10 mg. per ml. of solution.

Apparatus:

Colorimetric observations were made in a Coleman Junior Model Spectrophotometer using an adapter and small (10 x 75 mm.) cuvettes.

Determination of the Optimum Wavelength

Since it was planned to employ as a blank when making the readings a solution of the cobaltous acetate and isopropylamine in chloroform, the absorption curve of this mixture was first plotted.

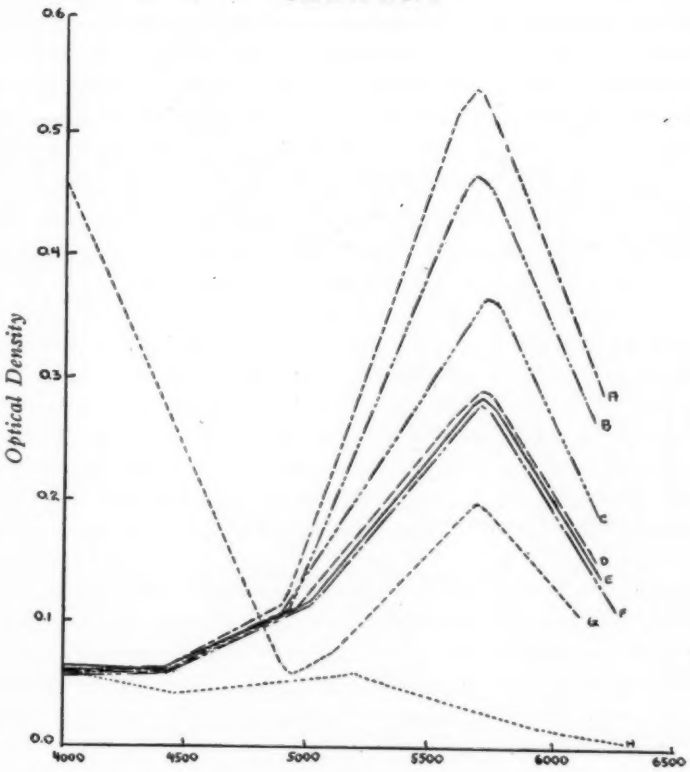
The readings were compared against a chloroform blank or control to determine if the colored reagents introduced the presence of any interference. The mixture was found to have an absorption maximum at a wavelength of 5200 A. The absorption curves of the different barbiturate drugs were then prepared, and compared both with a chloroform blank and a reagent blank or control. One ml. quantities of each of the barbiturate solutions were pipetted into cuvettes. To each cuvette was added the cobaltous acetate and isopropylamine solutions. Readings were made at varying wavelengths between 4000 A and 6000 A.

The results of these readings are summarized in Graph No. 1, where it will be noted that the maximum absorption, in terms of optical density $\left(-\log \frac{\text{Intensity (transmitted)}}{\text{Intensity (incident)}}\right)$ for each of the barbiturates occurred at a wavelength of 5650 A.

During the readings the cuvettes were stoppered with plain corks since evaporation of the chloroform resulted in a concentration of and a more intense color of the cobalt-barbiturate compound in solution. This, however, would have no effect on the absorption curve as this experiment was conducted to determine only the color and not the intensity of color. On the other hand, since it would affect the final readings, and hence the results in quantitative determinations, the routine practice of corking the cuvettes at all times was followed. It was noted that with the cuvettes corked to prevent evaporation, the color produced in the reaction was permanent and stable for at least one-half hour.

From Graph No. 1, it can be seen that Pentothal yielded a much greater absorption maximum at a wavelength of 4000 A than the peak obtained at a wavelength of 5650 A, indicating the presence of a yellow color component in the solution with an absorption maximum probably in the ultraviolet. It is possible that this yellow color component was caused by the sulfur in the Pentothal molecule, this compound being the only one of the seven barbiturates examined containing the "thio" grouping. Further studies would be required definitely to determine this fact. The color in the mixture of cobaltous acetate and isopropylamine in chloroform, as noted in Graph No. 1, does not materially affect the color produced during the reaction with the barbiturates.

GRAPH NO. 1



Wavelength (A)

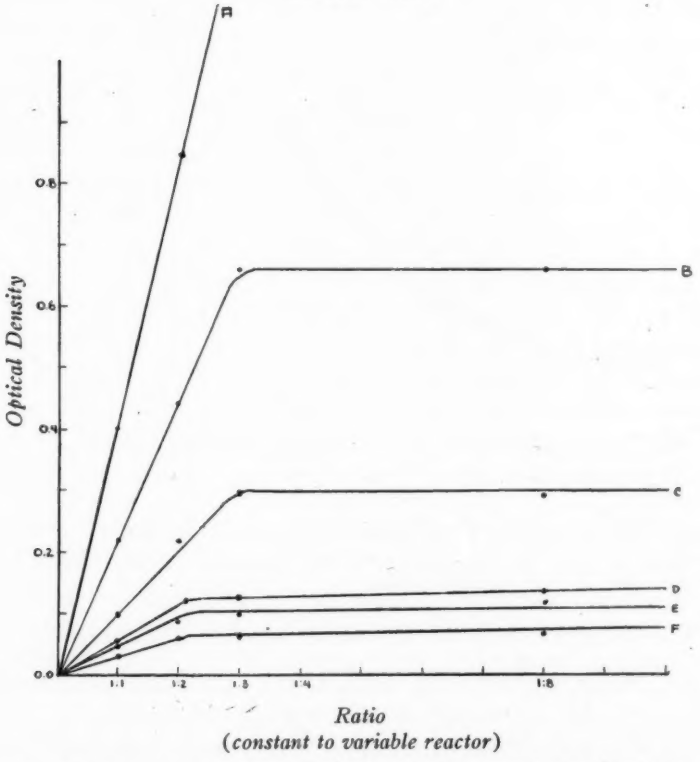
A—Barbital
B—Amytal
C—Seconal
D—Pentobarbital
E—Phenobarbital
F—Delvinal
G—Pentothal
H—Reagent "Blank"

Determination of the Optimum Reaction Quantities

The best wavelength for reading the barbiturate-cobalt color having now been determined, studies were undertaken to note the most suitable and effective quantities of cobaltous acetate and isopropylamine needed for the quantitative determination of the barbiturates. One ml. quantities of the chloroform solution of phenobarbital were used. This investigation was divided into two parts. In the first phase, varying amounts of the isopropylamine were added to the phenobarbital solution containing a definite and the same con-

stant quantity of cobaltous acetate solution. In the second phase, a definite and the same constant quantity of the isopropylamine solution was added to the barbiturate solution but the amount of cobaltous acetate added varied. Volumes of 0.05 ml., 0.1 ml., and 0.2 ml. were used for the reagent held constant, and the reagent which varied was added in amounts of twice, three times, four times and eight times that of the reagent held constant. Each of the mixtures was diluted to a volume of 3 ml. so as to maintain equal volumes in all tubes. The observations of these tests are summarized in Graph No. 2.

GRAPH NO. 2



A—Cobaltous Acetate Constant (0.2 ml.); Isopropylamine Variable.
B—Cobaltous Acetate Constant (0.1 ml.); Isopropylamine Variable.
C—Cobaltous Acetate Constant (0.05 ml.); Isopropylamine Variable.
D—Isopropylamine Constant (0.2 ml.); Cobaltous Acetate Variable.
E—Isopropylamine Constant (0.1 ml.); Cobaltous Acetate Variable.
F—Isopropylamine Constant (0.05 ml.); Cobaltous Acetate Variable.

Variations of the isopropylamine content with constant amounts of cobaltous acetate produced maximum color intensity for a given quantity of barbiturate when the ratio of one volume of cobaltous acetate to three volumes of isopropylamine was used. There was no reduction in the color intensity when isopropylamine was added beyond the optimum ratio, providing the total volume in all tubes. The mained the same. Less color intensity was produced for a given amount of barbiturate when constant amounts of isopropylamine solution were employed, but the amount of cobaltous acetate solution was varied. The addition of larger amounts of cobaltous acetate increased slightly the intensity of color produced, but this was due to the addition of the larger amounts of the pink-colored cobalt solution. As larger amounts of the solution of cobaltous acetate were added, the color hue also changed as a result of an admixture of the colored cobalt solution with a different colored compound due to the cobalt-barbiturate reaction. Substantially the same curves, with the same optimum ratio of cobaltous acetate to isopropylamine, were obtained when solutions of barbital and pentobarbital were substituted for the phenobarbital.

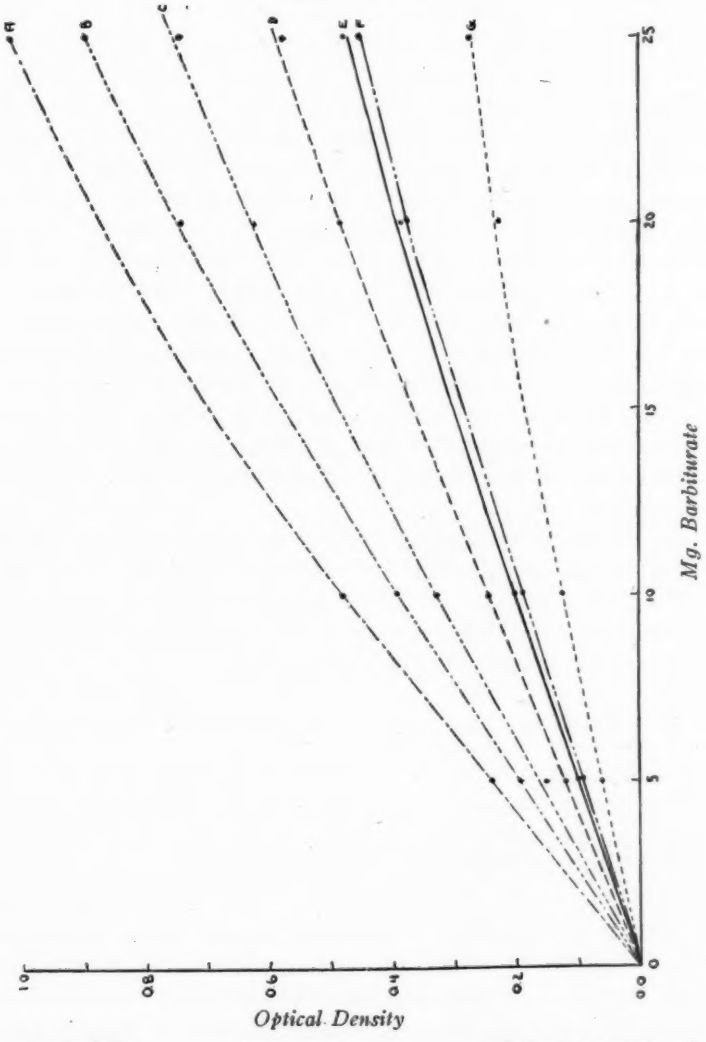
As a result of these preliminary studies, quantitative determinations of the barbiturates were thereafter performed at a wavelength of 5650 A, employing 0.2 ml. of the 1 per cent cobaltous acetate solution and three times that quantity of the 1 per cent isopropylamine solution for the maximum color development.

The Relation of Color Intensity to Barbiturate Concentration

Solutions of each of the barbiturates in chloroform were prepared in concentrations of 1 to 10 mg., and 15, 20 and 25 mg. per ml. of solution. This range of concentration was chosen since a survey of the literature of fatal cases of barbiturate poisoning revealed that these amounts would cover most cases. One ml. of each solution was pipetted into cuvettes. Two-tenths of a ml. of cobaltous acetate solution followed by 0.6 ml. of isopropylamine solution was added to each cuvette. The cuvettes were corked and inverted several times to insure thorough mixing. Readings were made at 5650 A against a reagent blank or control. The concentration-optical density curves produced are shown in Graph No. 3.

It will be noted from this graph that all of the seven barbiturates in concentrations of 1 to 10 mg. yielded practically straight lines.

GRAPH NO. 3



A—Barbital
B—Amytal
C—Seconal
D—Pentobarbital
E—Phenobarbital
F—Delvinal
G—Pentothal

Above concentrations of 10 mg. Barbital, Amytal and Seconal revealed a marked flattening of the respective curves. This flattening was not as pronounced with the other barbiturates. The above procedure can be used when determining amounts of barbiturates in a range between 1 and 10 mg. Above this concentration, it is necessary to dilute the chloroform barbiturate solution, so as to bring the amount of color produced within the range of proportionality.

In repeating the tests it was found that while the intensity of color to concentration held true for the lower barbiturate concentrations, the amount of color produced nevertheless varied somewhat on different runs of the tests. It was therefore apparent that the color produced per concentration of barbiturate varied slightly with test conditions so that if quantitative determinations were desired, calibration curves could not be used. Barbiturate standards must be employed simultaneously with each determination.

From Graphs 1 and 3, it can be noted that the various barbiturates do not produce the same amount of color per unit concentration. In attempting to determine if the amount of color produced by the different barbiturates was proportionally the same from day to day, additional tests were performed over a period of three months on the several compounds. Had this actually occurred, it would have been possible to employ as a standard any of the barbiturates for the quantitative determination of all barbiturates. These studies however were negative so that it is not possible to use such a procedure. The summary of these tests is shown in Tables No. 1 and No. 2.

TABLE NO. 1

Barbiturate	Molecular Weight (7) (12) (13)	Order of Color Intensity per Unit Concentration*
Barbital	184.109	1
Delvinal	224.254	6
Phenobarbital	232.109	5
Amytal	236.156	2
Pentobarbital	236.156	4
Seconal	238.280	3
Pentothal	242.330	7

* These figures represent the order of magnitude of the optical density readings. The figure 1 represents the highest optical density reading per unit concentration, 2 the next highest, etc.

TABLE NO. 2

Variations of Color Extinction Readings per Concentration

Barbiturate	5 mg.	10 mg.	20 mg.
Barbital	.240	.475	.842
	.244	.480	.853
	.236	.478	.847
	.241	.483	.850
	.232	.476	.841
	.251	.482	.856
	.248	.480	.845
	.242	.472	.838
	.246	.475	.850
	.237	.486	.844
Seconal	.165	.334	.628
	.158	.325	.620
	.161	.328	.622
	.155	.330	.634
	.153	.335	.631
	.158	.330	.630
	.150	.325	.633
	.164	.336	.633
	.160	.330	.628
	.154	.328	.625
Phenobarbital	.105	.200	.382
	.092	.208	.390
	.102	.197	.387
	.109	.192	.387
	.100	.198	.392
	.103	.204	.394
	.098	.197	.385
	.104	.206	.390
	.102	.201	.387
	.105	.198	.392
Pentothal	.064	.124	.228
	.060	.121	.225
	.058	.120	.225
	.065	.125	.221
	.060	.123	.226

Barbiturate	5 mg.	10 mg.	20 mg.
	.061	.126	.230
	.069	.129	.233
	.070	.131	.237
	.062	.128	.226
	.066	.127	.231
Amytal	.198	.391	.740
	.195	.398	.747
	.205	.407	.752
	.200	.398	.748
	.192	.394	.750
	.190	.391	.742
	.208	.406	.758
	.203	.400	.756
	.200	.398	.751
	.194	.392	.743
Pentobarbital	.124	.256	.487
	.120	.247	.483
	.128	.241	.480
	.117	.250	.485
	.119	.243	.476
	.121	.248	.473
	.124	.248	.482
	.126	.250	.477
	.125	.241	.481
	.123	.249	.483
Delvinal	.098	.195	.376
	.092	.190	.370
	.102	.200	.384
	.096	.195	.380
	.098	.199	.381
	.097	.192	.379
	.104	.199	.374
	.105	.206	.388
	.100	.203	.382
	.099	.200	.387

While the order of color intensity produced per unit concentration of barbiturate was generally the same throughout the tests, there

was no definite relationship between the intensity of color of any two barbiturates from day to day. Therefore, the possibility of using a factor based on the ratio of molecular weights, as is practiced in the determination of the sulfonamide drugs by the Marshall method, could not be followed. It was apparent that individual barbiturate standards would be required, unless, as is frequently the case in practice, the results could be reported in terms of a barbiturate equivalent using one of the most common barbiturates, such as phenobarbital. In all later studies, a 5 mg. standard of the individual barbiturates was employed in quantitative determinations.

Part II

Isolation, Identification and Quantitative Determination of Barbiturates

In most instances in hospital and clinical laboratories, qualitative barbiturate determinations only are requested. The physician is interested only in whether or not one of the barbituric acid derivatives is present in the body fluid submitted, usually blood or urine. In some cases, however, where the identification of the specific barbiturate is desired, or where the exact amount of barbiturate present is required, or in post-mortem and medico-legal examinations where speed is not of the utmost importance, further studies must be conducted.

For these cases, it is necessary to make allowances for the training of the technicians and the equipment available. These studies therefore concern themselves with the presentation of a simple procedure for the identification and quantitative estimation of the barbiturate present in body fluids and tissues which take these requirements into consideration.

Various procedures have been advocated for the extraction and isolation of barbiturate compounds from body fluids and tissues. Most workers originally followed the classic Stas-Otto method (14). Later, various modifications of this procedure were advanced, each of which was regarded as yielding a more complete recovery with less interference from extraneous substances. Koppanyi (5) suggested the use of 5 per cent potassium hydroxide solution to liquefy the tissues, followed by precipitation of the protein matter with copper sulfate. Later, Koppanyi, Veitch and Green (15) suggested the use of Lloyd's reagent for the removal of extraneous color in the extrac-

tion of the barbiturates. Brundage and Gruber (16) recommended the adsorption of barbiturate compounds from aqueous solutions by the use of activated charcoal. Kozelka and his co-workers (9) extracted the barbiturates by the use of 20 per cent acetic acid, neutralized the acetic acid solution to a pH of approximately 6.5 with sodium hydroxide solution, and then extracted the barbiturates with ether.

All of these different methods of extraction were tried repeatedly. It was found that the Stas-Otto technique, with minor modifications and using controls, would yield results as significant as any of the other suggested methods, and of great import was the fact that it was possible to utilize simple and readily available equipment.

The following procedure for the extraction of the barbiturates from body fluids and tissues is essentially the Stas-Otto method with modifications as noted.

In order to have definite quantities of barbiturate in tissues and fluids for recovery procedures, studies were not made by feeding barbiturates to animals, and subsequently extracting the barbiturates from the tissues. Instead, definite quantities of the various barbiturates were added to samples of hashed animal tissue, urine, or oxalated whole blood. Pieces of rabbit or guinea pig liver, kidney, brain and heart tissues were taken from freshly killed animals, frozen in dry ice until ready for use, and then hashed together in a Waring blendor. To the hash there was added separately at different occasions a measured quantity of solutions of the various barbiturates in 0.1 N sodium hydroxide. The hash was again mixed in the Waring blendor to give a uniform mixture, and the specimens were then ready for extraction.

The hashed tissue, or fluid, to which the barbiturate had been added was made acid to litmus with a saturated solution of tartaric acid. An equal volume of 50 per cent ethyl alcohol was added, the mixture well mixed, and then allowed to stand overnight in an incubator at 37.5° C. The mixture was then strained through gauze to remove gross particles. After checking to see that the material was still acid to litmus, 50 per cent alcohol was again added to the residue on the gauze, and extraction and straining was carried out as before. A third extraction with 50 per cent alcohol was performed on the acid residue. The 50 per cent alcoholic extracts were pooled, filtered through paper, and placed in a large, shallow dish. The liquid was evaporated on a water bath at a temperature of 55-60° C. Care

was taken that the temperature of the bath did not rise above 60° C. since it was found that this resulted in a loss, due to destruction, of some of the barbiturate. A current of air playing on the surface of the liquid, or an inverted funnel attached to an aspirator pump placed over the dish, was used to speed evaporation. When the residue was of a syrupy consistency, the acidity was again checked, and 100 ml. of absolute ethyl alcohol were added. The mass was stirred to bring about solution and increase the rate of precipitation of protein and extraneous matter. The alcoholic solution was poured off, and the dish washed with two 50 ml. portions of absolute alcohol. The pooled alcohol solutions were filtered through paper. The residue on the filter paper was washed with an additional 50 ml. of absolute alcohol and the washings were added to the other pooled alcoholic solutions. This mixture was then evaporated to a syrupy consistency as above. The residue was dissolved in about 100 ml. of 0.5 N sulfuric acid and allowed to stand for one hour, following which it was placed in a separatory funnel. Since it was known that alcohol will extract lipoidal material along with the barbiturate, the sulfuric acid solution was first extracted with three 25 ml. portions of petroleum ether in which the barbiturates are practically insoluble.

The solubility of the barbiturates in petroleum ether was checked in the following manner: Petroleum ether which had been filtered was added to accurately weighed quantities of each of the seven barbiturates, shaken, and allowed to stand for several minutes. A piece of filter paper was washed in petroleum ether, dried, and weighed. The mixture of barbiturate and petroleum ether was filtered through the filter paper, and the paper and residue dried and weighed. No appreciable loss was noted in the weight of the barbiturate after petroleum ether treatment. It is noted that Ozburn in his paper (10) which was published late in 1945, also used petroleum ether for lipoid removal.

Following fat extraction, the sulfuric acid solution was extracted with four 50 ml. portions of chloroform. At this point the extracts were usually clear and colorless. In some instances, however, traces of color were present in the chloroform solutions which in subsequent steps usually interfered with the determinations. The following procedure was introduced to eliminate this interference and this treatment was used routinely regardless of whether or not color was readily visible in the chloroform extracts. The latter were pooled

and chilled on an ice bath for five minutes. One gram of activated charcoal (USP) and 5 grams of anhydrous sodium sulfate (CP) were added to the chilled chloroform solution to remove color and moisture. This mixture was shaken for one or two minutes while on the ice bath, and then filtered through a fat-free filter paper while cold. The filtrate was evaporated on a water bath in a hood or under an inverted funnel attached to an aspirator pump at a temperature not exceeding 55-60° C. When the volume of the chloroform solution was about 4 or 5 ml., it was transferred to a sublimation tube, described below, with the aid of an additional 5 ml. of chloroform. The chloroform was evaporated under reduced pressure and sublimation carried out as described later.

The sublimed barbiturate was washed from the walls of the sublimation tube with a small quantity of ether which had been previously dried over anhydrous sodium sulfate. The ether solution was diluted to 25 ml. in a volumetric flask. A measured aliquot was allowed to evaporate under reduced pressure, when the barbiturate would crystallize out, usually in white crystals. In some few cases, resublimation and crystallization were necessary to obtain a pure product. Melting point determinations for the identification of the specific barbiturate were carried out in a suitable apparatus, such as that described in the United States Pharmacopœia or a melting point tube of the Thiele-Dennis type. The melting points of the barbiturate compounds are shown in table No. 3.

TABLE NO. 3

MELTING POINTS OF THE BARBITURATE DRUGS

Barbiturate	Melting Point (°C.)
Seconal	96 to 100
Pentobarbital	127-130
Amytal	153-155
Pentothal	156-159
Delvinal	162-163
Phenobarbital	174-178
Barbital	188-192

Following the identification of the specific barbiturate, the remainder of the ether solution (a known volume) was poured from the flask, the latter washed with additional portions of dried ether, and the ethereal solution allowed to evaporate to dryness.

The residue from the ether solution was then dissolved in 2 ml. of dry chloroform. One ml. of this solution was pipetted into a cuvette. To the solution in the cuvette were added 0.2 ml. of 1 per cent cobaltous acetate in absolute methanol and 0.6 ml. of 1 per cent isopropylamine in absolute methanol. The cuvettes were corked; the contents mixed by inversion, and the color produced compared against a 5 mg. standard of the specific barbiturate with a reagent solution as blank or control. Calculations were carried out as follows to determine the barbiturate content of the extract solution:

$$\frac{ODx}{ODs} \times 5 \times \frac{25}{A} \times 2 = \text{mg. barbiturate extracted}$$

where

ODx is the optical density reading of the extract.
ODs is the optical density reading of the standard.
A is the aliquot remaining in the flask.

Determinations were made on the extractions from tissues, blood and urine, each containing separately each of the seven barbiturates listed previously. The results of these tests are shown in Table No. 4.

TABLE NO. 4

Barbiturate	Material	mg. Barbiturate Added	mg. Barbiturate Recovered	Per cent Recovery
Seconal	Tissues	20.0	19.6	98
"	"	25.0	23.5	94
"	"	20.0	20.4	102
"	Blood	10.0	9.3	93
"	"	12.0	11.5	96
"	Urine	15.0	15.2	101
"	"	18.0	17.0	94.5
Phenobarbital	Tissues	18.0	18.5	103
"	"	40.0	31.0	77
"	"	20.0	18.9	94.5
"	"	30.0	30.1	100.5
"	"	15.0	14.0	93.3
"	Blood	20.0	19.2	96
"	"	35.0	30.1	86
"	"	25.0	24.3	97
"	"	20.0	19.7	98.5
"	Urine	50.0	49.3	98.6
"	"	40.0	38.0	95
"	"	15.0	15.3	102

Barbiturate	Material	mg. Barbiturate Added	mg. Barbiturate Recovered	Per cent Recovery
Pentothal	Tissues	12.0	12.3	102.5
"	"	20.0	18.6	93
"	"	20.0	19.1	95.5
"	"	10.0	9.6	96
"	Blood	7.0	6.5	92.8
"	"	12.0	11.8	98.4
"	Urine	15.0	14.4	96
Delvinal	Tissues	10.0	9.4	94
"	"	15.0	14.3	95.5
"	"	30.0	29.4	98
"	Blood	5.0	4.7	94
"	Urine	10.0	9.7	97
"	"	15.0	14.4	96
Pentobarbital	Tissues	16.0	16.4	102.5
"	"	25.0	15.0	60
"	"	15.0	15.5	103
"	"	20.0	19.2	96
"	"	10.0	9.4	94
"	Blood	25.0	24.7	99
"	"	10.0	7.2	72
"	"	18.0	17.5	97.2
"	Urine	10.0	9.4	94
"	"	15.0	12.6	84
"	"	20.0	18.6	93
"	"	30.0	29.1	97
Barbital	Tissues	25.0	24.6	98.5
"	"	40.0	37.4	93.5
"	"	45.0	43.3	96
"	"	30.0	30.2	100.5
"	"	15.0	14.2	94.8
"	Blood	15.0	15.1	100.6
"	"	20.0	19.2	96
"	Urine	25.0	24.8	99
"	"	10.0	10.3	103
"	"	40.0	40.1	100.3
Amytal	Tissues	30.0	29.1	97
"	"	40.0	37.6	94
"	"	25.0	24.6	98.5
"	Blood	20.0	20.7	103.5
"	"	10.0	9.5	95
"	Urine	50.0	48.0	96
"	"	20.0	20.1	100.5
"	"	35.0	32.9	94

In only five of a total of sixty-two tests were recoveries of less than 93 per cent obtained. In three of these five tests, made at the beginning of this study, and using pentobarbital, recovery ranged from 60 to 84 per cent. This was probably due to the fact that the temperature during evaporations was allowed to approach 80-90° C. In later examinations, using the same barbiturate, a proper control of the temperature resulted in higher percentage recoveries. In the other two tests of the five yielding results outside the recovery range as given by the majority, the chloroform solutions, of two determinations using phenobarbital, were deliberately not chilled before and during color removal with activated charcoal. In these tests recoveries of 77 and 86 per cent were obtained.

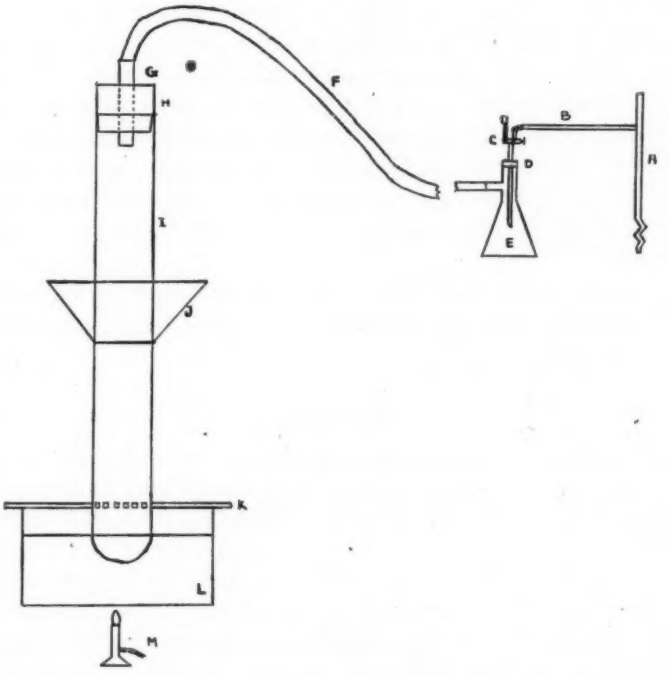
Purification of the Barbiturate by Sublimation Procedures

Of the various methods for purifying the barbiturates prior to identification by melting point determination, sublimation has proved best. However, most apparatus for conducting sublimations, which allow good recovery, are too complex and expensive for the small laboratory. Attempts were therefore made to devise an apparatus which could be simply and economically constructed in most laboratories.

The apparatus consists of a pyrex glass tube, such as is used for the digestion of filtrates in blood nitrogen determinations. This tube is approximately 25 x 200 mm. About half way down the tube, a glass, cup-shaped collar is annealed to the glass. The collar may be made from a small glass evaporating dish or from a weighing bottle with a hole cut in the bottom. If glass working apparatus is not available, a satisfactory collar can be made by placing a one-half inch piece of rubber tubing over the pyrex tube, and sliding a small glass evaporating dish with a hole in the bottom just wider than the diameter of the glass tube over the rubber sleeve. Care should be taken that the joint is as tight as possible. A one-hole rubber stopper containing a short length of glass tubing is inserted into the open end of the tube. To the glass tubing is attached a length of pressure rubber tubing leading, through a trap, to an aspirator pump. The sublimation tube is suspended, through a hole in a piece of asbestos board, into a liquid petrolatum oil bath or over a micro burner. The asbestos board is to prevent the heating of the upper walls of the

sublimation tube. The apparatus is shown in Figure No. 1, with the sublimation tube and its connections exaggerated in size.

FIGURE NO. 1



A—Aspirator Pump
B—Rubber Tubing
C—Two-way Stopcock
D—One-hole Rubber Stopper
E—Filter Flask
F—Rubber Tubing
G—Glass Tubing
H—One-hole Rubber Stopper
I—Pyrex Tube
J—Glass Collar
K—Asbestos Board with hole to fit pyrex tube
L—Oil Bath
M—Hot Plate or Flame

In carrying out the sublimation, the impure residue is placed in the bottom of the pyrex tube. The collar is filled with finely chipped ice to act as a condenser for the sublimed barbiturate. Suction is applied to create a partial vacuum, and the tube is heated in the petrolatum bath. As the barbiturate sublimes, it will crystallize on the walls of the tube in the region of the collar. It may then be scraped from the walls of the tube with a small spatula if only a few

crystals are desired, or washed from the walls of the tube with a small quantity of ether if the entire sublimate is desired. The barbiturate can be recovered by evaporation of the ether. Melting point and other determinations can then be carried out.

In this investigation, difficulty was encountered in obtaining crystalline Seconal. This barbiturate tended to collect in the "collar region" of the sublimation tube in small, oily globules. The same globules would appear on evaporation of the ether solution. (This serves as a possible identifying characteristic of this compound.) In such cases, the Seconal was washed from the walls of the tube with ether, the ether evaporated, and the barbiturate crystallized by the method given by the manufacturers in "New and Non-Official Remedies."

Mixed melting point determinations with pure barbiturates revealed that the apparatus described above performed the purification simply and well.

Summary

The following studies were conducted:

1. The best conditions for obtaining the barbiturate-cobalt color reaction.

2. The determination of whether or not the barbiturate-cobalt color reaction was proportional to the concentration of barbiturate thereby making the reaction suitable for quantitative determinations of barbiturates in body fluids and tissues.

3. Whether any one barbiturate could be used as a standard for the quantitative determination of all barbiturates.

4. The possibility of using a factor based on the ratio of molecular weights instead of using positive or known controls for each determination.

5. To devise a simple procedure, suitable for use in small hospital or clinical laboratories, for the isolation, identification and quantitative determination of the barbiturates in body fluids and tissues.

As a result of the studies reported here it was found that the barbiturate-cobalt reaction could be used for quantitative estimations and that the optimum wavelength for the measurement of the color

compound produced in the barbiturate-cobalt reaction is 5650 A, employing 0.2 ml. of a 1 per cent cobaltous acetate solution in absolute methanol and 0.6 ml. of 1 per cent isopropylamine in absolute methanol. Read at this wavelength, the color of the reacting agents does not interfere with the color produced in the reaction, and at concentrations of 1 to 10 mg. of barbiturate per ml. of chloroform solution, the color produced in the reaction was proportional to the barbiturate content.

It is not possible to employ one barbiturate as a standard for the quantitative determination of all barbiturates. In like manner, a factor based on the ratio of molecular weights, as is practiced in the determination of the sulfonamide drugs, cannot be employed in the case of the quantitative estimation of the barbiturates.

A procedure was devised, based on the Stas-Otto method for the extraction of the barbiturate drugs from animal tissues, whole blood and urine, requiring a minimum of apparatus and technical skill. By this procedure, recoveries of the barbiturate compounds from tissues and fluids of 93 per cent or more were obtained in fifty-seven extractions. Possible sources of error were noted and recorded.

A simple apparatus was also devised for the purification of the barbiturate drugs by sublimation, prior to identification by melting point and other determinations.

Acknowledgment

Appreciation is expressed for the assistance and helpful suggestions made by Dr. Louis Gershenfeld in the preparation and drafting of this paper.

BIBLIOGRAPHY

(1) Parri, W.: *Boll. Chim. Farm. 63,* 401 (1924).

(2) Zwikker, J. J. L.: *Pharm. Weekblad 68,* 975 (1931).

(3) Bodendorf, K.: *Arch. d. Pharm. 270,* 291 (1932).

(4) Koppanyi, T., Murphy, W. S., and Krop, S.: *Proc. Soc. Exp. Biol. and Med. 30,* 542 (1933).

(5) Koppanyi, T., Murphy, W. S., Krop, S., and Dille, J. M.: *J. Amer. Pharm. Assoc. 23,* 1074 (1934).

(6) Kozelka, F. L., and Tatum, H. J.: *J. Pharm. and Exp. Therap. 59,* 54 (1937).

(7) *United States Pharmacopoeia XII,* pages 78, 349, 355. Mack Prtg. Co. (1942).

(8) Motley, H. L.: *J. Missouri St. Med. Assoc. 38,* 228 (1941).

(9) Kozelka, F. L., Nelson, D. E., and Tatum, H. J.: *J. Pharm. and Exp. Therap. 67,* 70 (1939).

(10) Ozburn, E. E.: *U. S. Nav. Hosp. Corps Quart. 18,* 49 (1945).

(11) Front, J.: *Amer. J. Clin. Path., Tech Sup. 1,* 160 (1940).

(12) *New and Non-Official Remedies,* pages 504, 518, 527. Amer. Med. Assoc. (1945).

(13) Manufacturers Literature.

(14) Autenreith and Warren: "Detection of Poisons." P. Blakiston's Sons and Co. (1928).

(15) Koppanyi, T., Veitch, F. P., and Green, M. W.: *J. Amer. Pharm. Assoc. 32,* 309 (1943).

(16) Brundage, J. T., and Gruber, C. M.: *J. Pharm. and Exp. Therap. 59,* 379 (1937).

SIR KENELM DIGBY AND THE POWDER OF SYMPATHY

By Wyndham Miles *

ONE of the most peculiar men who dabbled in science during the late Renaissance was an eccentric Englishman named Kenelm Digby. Digby is almost unknown today; yet, during the 17th century he was famous throughout England both as a scholar and as an adventurer. Digby was a many-faceted genius. He wrote treatises on alchemy, metaphysics, philosophy and natural history, and among other things was an English Admiral, and Chancellor to the Queen. One of Digby's most famous creations was a quack medical remedy which he called "The Powder of Sympathy," and it is this sympathy cure which we intend to make the main topic of this paper.

Sir Kenelm Digby was born in 1603, the son of the rebellious Englishman Everard Digby, who was executed for complicity in the Gunpowder Plot. In his youth he studied at Oxford for two years, but there is no record that he received a degree from that school. After leaving Oxford in 1620, Digby traveled extensively on the continent, visiting France, Italy and Spain. While in Madrid, Digby became acquainted with Prince Charles of the English royal family, and the friendship springing from this meeting may have been one of the reasons why Digby was knighted upon his return to England in 1623.

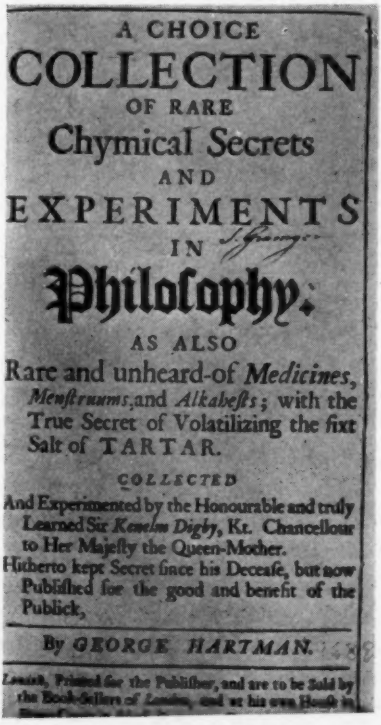
In 1625, he married Venetia Stanley, who, from all accounts, was a very beautiful English girl, and for the next two years lived a quiet life away from the court. In 1627, Digby took out letters of marque from the Duke of Buckingham and set sail with two ships for the Venetian harbor of Scanderoon where he intended to capture the French vessels which usually lay there at anchor. En route, he captured several Flemish and Spanish ships in some sharp fighting off Gibraltar, and a Dutch vessel at Majorca. The expedition finally arrived at Scanderoon in June, 1627, and after a fierce battle Digby overcame the French and Venetian vessels that had been lying in the harbor. News of this victory was received with great

* Instructor in Chemistry, The Pennsylvania State College.

Engraving of Digby by Houbraken, from a portrait by Vandyke.

enthusiasm in England, and was one of the reasons for Digby's later success in politics.

In 1633, Lady Digby died. A rumor soon spread that Kenelm had accidentally poisoned his wife by insisting that she drink viper-wine to preserve her beauty. Whether this rumor was true or not, Digby went into seclusion for two years as a sign of mourning. It was during this period of seclusion at Gresham College that he began to dabble in alchemy. Many of his alchemical recipes were published posthumously in London, in 1682, by his laboratory assistant, George Hartman.


A CHOICE
COLLECTION
OF RARE
Chymical Secrets
AND
EXPERIMENTS
IN
Philoſophy.
AS ALSO
Rare and unheard-of *Medicines*, *Menſtruums*, and *Alkahests*; with the True Secret of Volatilizing the fixt Salt of TARTAR.
COLLECTED
And Experimented by the Honourable and truly Learned Sir *Kenelm Digby*, Kt. Chancellour to Her Majeſty the Queen-Mother.
Hitherto kept Secret ſince his Deceaſe, but now Publiſhed for the good and benefit of the Publick,
By GEORGE HARTMAN.

The title page from Digby's "Alchemical Works," published in 1682.

From this time on Digby took an interest in politics and was in and out of office several times. His religious views got him into

serious trouble, which can be easily understood when the rapidly changing political conditions in England at that time are considered. He was finally imprisoned in 1642 for his catholic tendencies, and a year later was exiled to France.

While in France, Digby again took to alchemy and natural philosophy. In 1644 he published a volume containing two of his best known treatises, both intended for the education of his son. One of these, "The Nature of Mans Soule," is metaphysical. The other, "The Nature of Bodies," deals with natural philosophy, and is an excellent picture of the state of science in the days when the aristotelian philosophy was on its last legs but had not yet been entirely vanquished in spite of the discoveries and writings of such men as Galileo, Gilbert and Harvey.

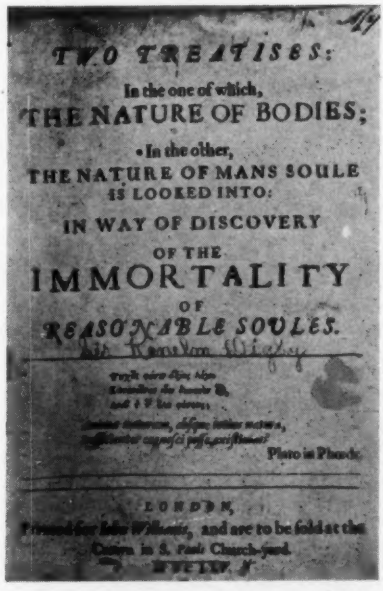
Digby was not an experimental scientist. Consequently, these treatises are a mixture of scholasticism, superstition and gullibility. Digby still clung to the aristotelian theory of the four elements, fire, air, water and earth, and the formation of these elements from cold and heat and humidity and dryness. He disagreed with Galileo's law that objects of different mass fell from the same height with the same velocity, and quoted old arguments of the aristotelians to prove that heavy objects fell faster than light ones. He thought that colors were formed from different proportions of black and white. Digby even records the story of a Spaniard who witnessed the spontaneous generation of a caterpillar-like insect from a stick lying in mud.

These two treatises were quite popular in their time. At least three other editions were published in London in 1645, 1665 and 1669.

Digby was finally allowed to return to England in 1653. In 1655 he left again and traveled on the continent, presumably undertaking various diplomatic missions for Cromwell. While at Montpellier, France, in 1658, Digby delivered a lecture on his so-called Powder of Sympathy.

Sympathy cures were a peculiar class of remedies developed during the late middle ages. Weapon salve, one of the best known of these sympathy cures, can be used to illustrate their use. When a person was wounded, the wound was cleansed and bandaged, while the weapon which had inflicted the wound was anointed with the weapon salve, and then bandaged and cared for as carefully as if it were flesh and blood, and not merely an inanimate object. The theory

behind this practice was that there existed a peculiar magnetism between the weapon and the wound, and if the weapon were nursed the wound would heal. It is obvious that any success the weapon salve might have had was due to the innate ability of wounds to heal when kept clean and uninfected; and cleansing and bandaging wounds


TWO TREATISES:
In the one of which,
THE NATURE OF BODIES;
In the other,
THE NATURE OF MANS SOULE
IS LOOKED INTO:
IN WAY OF DISCOVERY
OF THE
IMMORTALITY
OF
REASONABLE SOULES.
Sir Kenelm Digby
Plato in Phædr.
LONDON,
and are to be sold at the
Crown in S. Pauls Church-yard.

Title page of the 1665 edition of Digby's "Two Treatises."

gave them a better chance of healing in many cases than if they were handled and treated in the unsanitary manner of those times.

One disadvantage of weapon salves was that the weapon which inflicted the wound was often unobtainable. Weapon salves were also opposed by the clergy, who denounced them as being magical. The salves were often disgusting mixtures of such things as eunuch's fat, human blood and moss from the skulls of executed criminals.

Digby's Powder of Sympathy was, as he implies, a powder, not a salve. It was not used for wounds alone but as a remedy for other disorders as well. It had one advantage over weapon ointments, the physician did not have to have the weapon in order to treat the wound.

The Powder of Sympathy was nothing more than ordinary English vitriol—iron sulphate. Digby kept the composition of the Powder secret for some time and decided to make it public only after Dr. Mayerne, the physician of King James, became aware of it. Perhaps Digby was afraid that the influential Mayerne might claim the Powder as his own, which would not have been astonishing when the ethics of that time are considered.

Portrait of Digby from the 1665 edition of "Two Treatises."

Digby left behind a very complete account of his sympathy cure, perhaps the most complete account we have of such a remedy. His book seems to have been published first in London, in 1658, although the book is labeled second edition and is supposed to be a translation from the French. Several French editions were published subsequently, the ones of 1659, 1660, 1666 and 1681, being known to the author. Information on the Powder of Sympathy can also be found in later editions of the treatises on "The Nature of Bodies, and The Nature of Mans Soule."

According to Digby's tale, he had been traveling in Tuscany where he met a Carmelite friar who had journeyed from the east. This friar held the secret of the Powder of Sympathy, and had refused to divulge it, even to the Duke. Digby befriended the friar, who, to show his gratitude, gave him the secret of the sympathy cure. The story has not been taken seriously by historians, their objection being that Digby's account of the much publicized friar is not substantiated by contemporary writings. This tale may have been a convenient story invented by Digby to give credence to the magical properties of the Powder of Sympathy.

The most famous case involving the Powder of Sympathy was that of the English author, James Howell, who had been wounded while trying to separate two of his friends who were settling an argument with swords. Howell, who showed more impetuosity than good sense, rushed between the two swordsmen and tried to catch their blades. He received a serious cut on the hand. The duelers immediately dropped their weapons and tried to staunch the flow of blood from Howell's cut, one of them using a garter as a bandage. The wound showed no tendency to heal; one of King James' own physicians treated it without success. Howell at length became so alarmed over his wound that he sent for Digby and asked him to try his sympathy cure.

The treatment that Digby gave the wound was quite simple. He took the bloody garter that had first bound Howell's hand, and immersed it in a solution of the Powder of Sympathy. The basin holding the garter was kept at a moderate temperature by placing it in the sun during the day, and near a fire at night. Digby had Howell lay aside his plasters, and told him to keep the wound clean and at a moderate temperature. Sir Kenelm relates that this treatment was so effective that Howell's inflamed hand felt cool, as though a wet napkin had been placed on it, as soon as the garter was placed in the solution, and the wound again became inflamed if the garter were removed. The garter was left in the solution for five or six days and the wound healed uneventfully.

This case brought Digby and his sympathetic cure considerable publicity. King James finally persuaded Sir Kenelm to confide the secret of the powder in him, and from the King it was discovered by his observant physician, Dr. Mayerne. It was Dr. Mayerne's

discovery of the composition of the powder that caused Digby to publish his book.

Digby's explanation of the action of the powder was quite involved, but briefly it was this. The basin holding the solution of sympathy powder and the bloody bandage was placed in the sun during the day and near a fire at night, the object being to keep the solution and bandage at body temperature. The heat caused the atoms of the blood and the spirits of the vitriol to be thrown off into the air and at the same time caused the inflamed wound to exhale hot spirits. These ascending spirits caused a current to be set up in the air around the wound and the basin. This current swept the atoms of blood and the accompanying vitriol to their original source in the wound where they remained. The blood and vitriol worked together in the wound, which was comforted and imperceptibly healed. When a cicatrix had formed, the basin and its contents were no longer needed.

The method of preparing the Powder of Sympathy was quite simple. English vitriol was crystallized from water, dried, powdered, and then stored in a dark place until used.

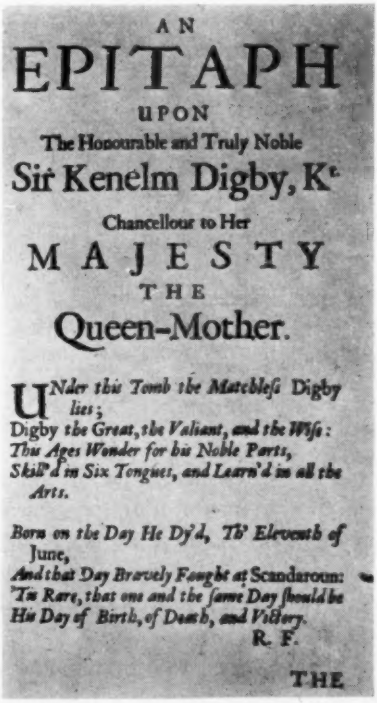
The usual method of using the powder was to dissolve it in water and then to add to this solution a bloody dressing. George Hartman, Digby's laboratory assistant, says that he had seen the sympathy cure used to heal green wounds, and to stop nose bleeds.

The use of sympathy cures died out slowly after Digby's time. They were attacked by both scientists and clergymen. For example, a small volume was published by William Foster, in London, in 1631, entitled "Hoplocrisma Spongus, or, A Sponge to wipe away the Weapon-Salve. A treatise, wherein is proved that the cure late-taken up amongst us, by applying the salve to the weapon, is Magicall and unlawfull."

Kenelm Digby's scientific reputation was very high during his time. This can be judged from the fact that he was on the council of the Royal Society when it was incorporated in 1663. In Anthony Wood's "Athenae Oxonienses," published in 1691, which was a history of all writers and bishops who had been educated at Oxford from 1500 to 1690, Digby was given more space than Robert Boyle. However, John Evelyn mentions him several times in his diary, where, with his usual discernment he wrote "Sir Kenelm was an arrant mountebank."

Digby died suddenly on June 11, 1665, and was buried beside his wife in Christ Church, Newgate.

In addition to the volumes of Digby's works previously mentioned, a "Theatrum Chimicum" was published in Amsterdam in 1693, "Medicinia Experimentalis Digbaeana" in Frankfurt in 1672, "Choice and Experimental Receipts in Physick and Chirurgery" in London in 1668, and works on religion and other subjects at various times.



AN

EPITAPH

UPON

The Honourable and Truly Noble

Sir Kenelm Digby, Kt.

Chancellour to Her

MAJESTY

THE

Queen-Mother.

UNder this Tomb the Matchleſs Digby *lies;*
Digby *the Great, the Valiant, and the Wiſe:*
Thus Ages Wonder for his Noble Parts,
Skill'd in Six Tongues, and Learn'd in all the Arts.

Born on the Day He Dy'd, Th' Eleventh of June,
And that Day Bravely Fought at Scandaroun:
'Tis Rare, that one and the ſame Day ſhould be
His Day of Birth, of Death, and Victory.
R. F.

THE

An Epitaph on Digby, from "A Choice Collection of Rare Chymical Secrets," edited by Hartman, 1682.

REFERENCES

Thomas Longueville, "Life of Kenelm Digby," by one of his Descendants, London, 1896.

Anthony Wood, "Athenae Oxonienses," 2 vols., Oxford, 1691-1692.

John Aubrey, "Brief Lives," edited by A. Clark, Oxford, 1898.

John Evelyn, "The Diary of John Evelyn," edited by A. Dobson, London, 1908.

S. L. Lee, "Kenelm Digby," Dictionary of National Biography, vol. 15, London, 1888.

SELECTED ABSTRACTS

The Synergistic Action of Penicillin and Mapharsen (Oxophenarsine Hydrochloride) in the Treatment of Experimental Syphilis. H. Eagle, H. J. Magnuson and R. Fleischman. *J. Venereal Dis. Inform. 27,* 3 (1946). Penicillin and mapharsen were observed to have a pronounced synergistic action in the treatment of syphilis produced experimentally in rabbits by intratesticular inoculation with the Nichols strain of *S. pallida.*

When penicillin sodium alone was given intramuscularly twice daily for four days, the total dosage required to cure 50 per cent of the animals (CD_{50}) was 44,000 units/Kg., that required to cure 90 per cent of them (CD_{90}) was 80,000 units/Kg.

Mapharsen alone, administered once daily for four days, had a CD_{50} dose of 2.4 mg./Kg. and a CD_{90} dose of 3.0 mg./Kg. A dosage level of 1 to 1.6 mg./Kg. cured only one of twenty-one animals.

In the experiments in which both drugs were administered, the daily intravenous injection of mapharsen was performed midway between two intramuscular injections of penicillin. It was found that the two drugs were chemically incompatible when present in high concentration *in vitro,* the penicillin undergoing slight but definite inactivation.

The administration of penicillin with subcurative doses of mapharsen (0.15 mg./Kg. daily for four days) was found to reduce the CD_{50} level of penicillin to 6,100 units/Kg. and the CD_{90} dose to 32,000 units/Kg. Larger, but still subcurative, doses of the arsenical (0.4 mg./Kg.) reduced the CD_{50} and CD_{90} doses of penicillin to 800 units/Kg. and 4,000 units/Kg., respectively.

Even more striking results were obtained in experiments in which penicillin sodium was injected intramuscularly at more frequent intervals, i. e., five times daily for four days. The CD_{50} and CD_{90} doses were 1,850 units/Kg. and 8,000 units/Kg., respectively. The concurrent administration of subcurative doses of mapharsen (0.4 mg./Kg. daily for four days) reduced the CD_{50} and CD_{90} doses of penicillin to 320 units/Kg. and 1,000 units/Kg., respectively.

Clinical studies are now in progress in which three groups of patients are to receive variations of the penicillin and mapharsen therapy. All three groups will receive both drugs, although different dosage levels will be used; in addition, bismuth subsalicylate will be administered to patients of two groups.

Streptomycin in the Treatment of Clinical Tuberculosis: Preliminary Report. H. C. Hinshaw and W. H. Feldman. *Proc. Staff Meet., Mayo Clinic 20,* 313 (1945); through *U. S. Naval Med. Bull. 46,* 91 (1946). Streptomycin has been used at the Mayo Clinic in the treatment of thirty-four tubercular patients, all with unfavorable prognosis. The intramuscular route of administration was preferred, but the drug was also given subcutaneously, particularly when less irritating preparations of it were available. Reactions were observed less frequently with streptomycin of greater purity.

The drug did not appear to have a rapidly curative action in sixteen cases of pulmonary tuberculosis in which it was given for a period of from one to three months. It was observed, however, that extensive and progressive lesions of known recent origin tended to improve promptly. Two cases of early miliary tuberculosis and one of renal tuberculosis showed marked improvement on X-ray examination, but not clinically. Six patients with cutaneous tuberculosis showed striking improvement.

The authors emphasize that no definite conclusions can be drawn from this preliminary study of a small series of cases, and that the toxic effects of protracted treatment remain in doubt. At the present time such measures of proved efficacy as proper care in a sanatorium and collapse therapy must not be discarded in favor of treatment with streptomycin or other antibiotic agents.

Globin Insulin: A Clinical Study. A. Trasoff, C. Borden and S. S. Mintz. *Am. J. Digest. Dis. 12,* 313 (1945); through *U. S. Naval Med. Bull. 46,* 24, 76 (1946). Examination of the literature

reveals that favorable results have been obtained through the administration of globin insulin to moderately severe diabetics who required one large dose of protamine zinc insulin alone for satisfactory control. In more severe cases which required separate injections of both protamine and regular insulin, globin insulin controlled the condition in only two of six patients.

Globin insulin may be advantageous in patients who have allergic reactions to protamine and in those subject to nocturnal hypoglycemia.

In the few papers which report clinical studies on the administration of globin insulin to patients who previously needed both protamine and regular insulin, the degree of regulation is judged by the absence of glycosuria rather than by blood sugar tests.

Snake Venom as a Therapeutic Agent. B. Mukerji and S. C. Ganguly. *Pharm. J. 102,* 26 (1946). Since ancient times in India and China snake venoms have been believed to possess great medicinal value, but their use in western medicine has come about only within the last fifteen years.

Cobra venom has been advocated for the relief of pain, particularly that of inoperable cancer, nerve leprosy, tic douloureux, and various conditions grouped under the name of "rheumatism" and "arthritis." Indifferent results have been obtained through its use in treating epilepsy and choreiform seizures.

The venom of the Russell viper has been recommended in the treatment of functional uterine bleeding, idiopathic epistaxis, thrombocytopenic purpura haemorrhagica and haemophilia, though its use in the latter condition is now largely discredited.

Preparations of both venoms have been marketed in India, Great Britain and the United States; the physiologically standardized solutions of these venoms produced by two American firms have not, however, received recognition in the N. N. R.

Nearly all snake venoms contain neurotoxin, haemolysin, haemorrhagin, proteolysin, lecithin, cholesterol, enzymes, etc., in concentrations and ratios which vary greatly in different species and even in specimens derived from the same snake under various conditions.

Collaborative research performed in India has resulted in data which serve as the basis for proposed standards for the venoms of the cobra and Russell viper. In part, these are summarized as follows:

Cobra venom is the dried secretion obtained from the poison glands of *Naja tripudians* and other species of *Naja* (Fam. *Colubridae*).

Viper venom (synonym: Daboia venom) is the dried secretion obtained from the poison glands of *Vipera russellii* and other species of *Viperae* (Fam. *Viperidae*).

In each case the poisonous secretion is dissolved in the minimum amount of ice-cold sterilized water and filtered. The filtrate is poured into an excess of ice-cold methanol, the precipitate collected by centrifugation and quickly dried in a vacuum desiccator over phosphorus pentoxide. All the above operations are performed under aseptic conditions.

The description of each venom is identical: an almost white or very light-yellow dry powder, soluble in water, and insoluble in methanol.

A solution of cobra venom produces, in the presence of lecithin, haemolysis of red blood corpuscles suspended in isotonic saline solution (distinction from viper venom).

A solution of viper venom produces coagulation of citrated human plasma (distinction from cobra venom).

Each venom is required to meet a purity test and also a biological assay for its toxicity, performed on pigeons.

The venoms are packaged in dry form in a single-dose ampul wrapped in black paper and stored in a cool, dry place protected from light.

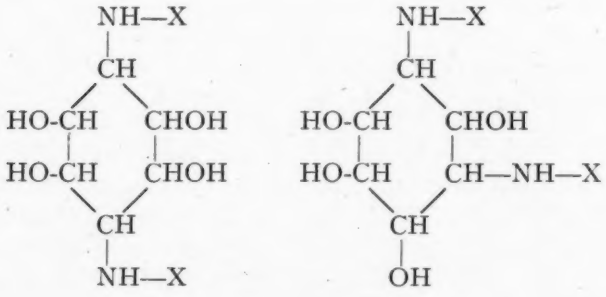
For administration, the contents of one ampul is to be dissolved in 1 mil of sterilized water immediately before use. Preliminary experiments have indicated that venom solutions are unstable and tend to precipitate on storage. Both venoms are injected intramuscularly; the adult dose, in each case, is from 0.01 to 0.03 mg. of cobra venom, in gradually increasing doses, and from 0.01 mg. to 0.2 mg. of viper venom. A solution of viper venom may also be used for local application, but it should never be administered intravenously.

Degradation of Streptomycin and the Structure of Streptidine and Streptamine. H. E. Carter, J. T. Alberi *et al.* *Science 103,* 53 (1946). Through the degradation of streptomycin hydrochloride by means of hydrogen chloride in methanol, the authors obtained guanidine and the hydrochloride of a nonguanidine base whose properties agreed with those of the "methyl streptobiosaminide dimethyl acetal hydrochloride" described by Brink *et al.*

Streptidine sulfate was obtained by the hydrolysis of streptomycin chloride with 1 N sulfuric acid. The alkaline hydrolysis of streptidine produced a new base, for which the name "streptamine" is proposed. This reaction is believed to occur as follows:

$$\underset{\text{Streptidine}}{C_8H_{18}N_6O_4} + 4H_2O \rightarrow \underset{\text{Streptamine}}{C_6H_{14}N_2O_4} + 4NH_3 + 2CO_2$$

The hexaacetyl, hexabenzoyl and N,N-dibenzoyl derivatives of streptamine were prepared and studied. Upon periodate oxidation, streptidine consumed two moles of the reagent; streptamine, six; dibenzoylstreptamine, two. No formaldehyde was formed from any of these compounds. From these observations and the analytical data, streptamine is believed to be either the 1,3- or the 1,4-isomer of diaminotetrahydroxycyclohexane. Accordingly, streptidine and streptamine may be provisionally assigned one of the two following formulae:



In Streptamine, X = H

In Streptidine, X = $-C\begin{matrix}/\!/NH \\ \backslash NH_2\end{matrix}$

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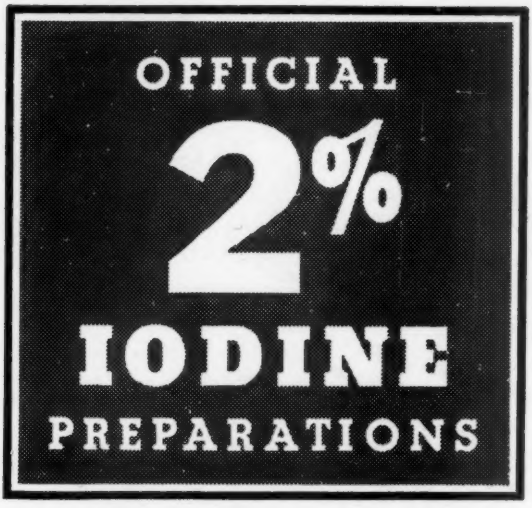

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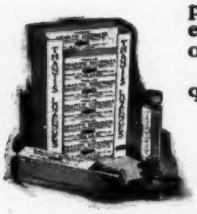

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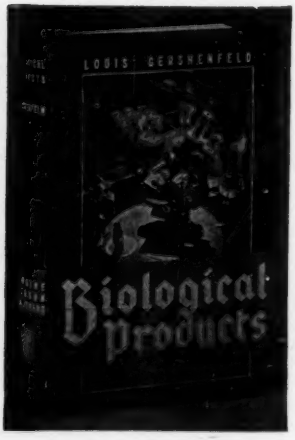

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